

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X17115

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

22 FEB 2006

| |
|---|
| Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) |
|---|

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

| | | |
|--|--|--|
| International application No. PCT/US2005/012191 | International filing date (day/month/year) 08.04.2005 | Priority date (day/month/year) 22.04.2004 |
|--|--|--|

| |
|--|
| International Patent Classification (IPC) or both national classification and IPC C07D401/12, C07D413/14, C07D207/08, C07D207/12, C07D403/12, C07D413/04, A61K31/401, A61P25/00 |
|--|

Applicant

ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx. 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Bosma, P

Telephone No. +31 70 340-3665



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

- The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
- This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012191

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|-------------------------------|------|--------|------|
| Novelty (N) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: WO 2004/024081 A (ELAN PHARMACEUTICALS, INC; PFIZER, INC; MAILLARD, MICHEL; BALDWIN, ERI) 25 March 2004 (2004-03-25)

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1-9, and describes (see examples and claims) acetyl 2-hydroxy-1,3-diaminoalkane derivatives as BACE inhibitors useful in the treatment of Alzheimer's disease.

The subject-matter of the present claims 1-9 differs structurally from these compounds a.o. (for the closest possibilities) in the restriction to **pyrrolidine** derivatives as depicted in formulae I and III.

The compounds in question are also useful as BACE inhibitors.

The intermediates of the present claim were not found in the prior art documents and online databases and therefore it is considered that the subject-matter of claims 1-10 is new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as the provision of further compounds useful as BACE inhibitors.

The solution to this problem proposed in claims 1-9 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: There were no incentives from the cited prior art to use the specific pyrrolidine derivatives of formulae I and III in order to modify the known compounds of D1 as BACE inhibitors, providing the subject matter according to claims 1-9 of the present invention.

An inventive step can also be recognised for the intermediates acc. to claim 10.

D1 does not disclose the oxazolidine type intermediates of formula IV, which contribute to the structural differentiation of the end-products over the state of the art (D1).

Re Item VII

Certain defects in the international application

- 1) Claim 1 comprises all the features of claim 9 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).
- 2) On page 2 the indicated patent application number WO 04/0039034 is not correct.